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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,273	12/13/1999	JORJ TERRY ULRICH	9950-0002	5731

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/402,273	Applicant(s) ULRICH ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/11/02; 6/17/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/11/02 has been entered.

2. Claims 1-2 and 6-8 are pending and are being acted upon in this Office Action.

3. In view of the amendment filed 3/11/02, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2 and 6-8 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* pharmaceutical composition capable of selectively enhancing a TH1 response comprising tyrosine, any allergen or any allergen extract, optionally modified by reaction with any cross-linking agent and 3-DMPL, (2) any composition mentioned above wherein the allergen is coated with and/or absorbed onto tyrosine.

The specification discloses only one modified allergen, that is, glutaraldehyde modified grass pollen extract, and one unmodified ovalbumin coated or absorbed with tyrosine (See page 4 of the specification). Furthermore, the term "optionally" implies that allergen needs not be modified. The specification as filed requires that the allergen be chemically modified (See page 4 of the specification). Other than the specific glutaraldehyde modified grass pollen extract and unmodified ovalbumin, there are no other modified and unmodified allergen or extract. Given the lack of any additional pharmaceutical composition capable of selectively enhanced a TH1

response comprising tyrosine, modified or unmodified allergen, modified or unmodified allergen extract and 3-DMPL, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/11/02 have been fully considered but are not found persuasive. Applicants' position is that (1) claim 1 now specified that the allergen or allergen extract is optionally modified by reaction with a cross-linking agent, (2) the preparation 1 on page 4 describes a modified grass pollen extract, and preparation 2 describes an unmodified ovalbumin allergen. (3) Although only glutaraldehyde is exemplified as a cross-linking agent, it would be readily appreciated by a person skilled in the art that any suitable crosslinking agent would suffice as indicated on page 2, lines 15 and 16 of the specification.

However, the claims encompass indefinite number of undisclosed modified or unmodified allergen. The specification discloses only one glutaraldehyde modified grass pollen allergen and one unmodified ovalbumin allergen. Further, the term "optionally" implies that allergen needs not be modified. However, the specification as filed requires that the allergen be chemically modified (See page 4 of the specification). Given the indefinite number of undisclosed modified or unmodified allergen for a pharmaceutical composition one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-2 and 6-8 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892).

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine and a modified allergen or allergen extract such as glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference allergen is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO 96/34626 publication teaches the reference pharmaceutical composition is useful for desensitization therapy of allergy sufferers (See claims 1-2, and 6-7 of the WO 96/34626 publication, in particular).

The claimed invention differs from the reference only by the recitation that the pharmaceutical composition comprises a 3-DMPL that capable of selectively enhancing TH_1 response.

The WO 92/16556 publication (Van Wijnendale et al) teaches a pharmaceutical composition comprising 3-DMPL, which is an adjuvant for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH) by injection (See page 22, example 2a, pages 24-25, pages 28-29 claim 9 of WO 92/16556, in particular) and an antigen such as gp160. The WO 92/16556 publication further teaches that the adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response wherein the DTH immune response is a TH1 response (See page 29, lines 8-16, in particular).

The '862 patent teaches a therapeutic composition comprising un modified allergen such as isolated flea saliva protein and an adjuvant such as Ribi adjuvant from Ribi ImmunoCHem

which is 3-DMPL that enhances the immune response to any antigen (See column 42, line 20-35, claims 22 and 24 of '862, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant as taught by the WO 92/16556 publication in a pharmaceutical composition comprising tyrosine and modified allergen for desensitization therapy as taught by the WO/9634626 publication or substitute the unmodified allergen as taught by the '862 patent for the modified allergen as taught by the WO 96/34626 publication for a pharmaceutical composition comprising tyrosine, allergen or allergen extract, optionally modified with a crosslinking agent and 3-DMPL as taught by the WO 96/34626 publication, WO 92/16556 publication and the '862 patent. From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 92/16556 publication teaches that the adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response where DTH is a TH_1 response (See page 29, lines 8-16, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized allergen is useful for desensitization therapy of allergy sufferers since glutaraldehyde modified allergen reduces the antigenicity of said allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular). The '862 patent teaches unmodified allergen and adjuvant such as Ribi adjuvant, which is 3-D MPL is useful in desensitization therapy because it enhances the host immune response to any allergen (See claims 22 and 25 of '862 patent, column 4, lines 19-21 and 30-33, sentence spanning from column 7 bridging column 8, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

Applicants' arguments filed 3/11/02 have been fully considered but are not found persuasive. Applicants' position is that (1) the invention is based on the observation that 3-DMPL can enhance the TH_1 over TH_2 directing properties of administered allergens and that the

adjuvant combination of tyrosine and 3-DMPL is surprisingly synergistic, (2) Wheeler et al discloses a pharmaceutical composition comprising tyrosine and a polymerized (optionally modified) allergen, but does not discloses 3-DMPL, (3) Van Wijnendale et al discloses a vaccine formulation containing gp 160 and 3-DMPL where 3-DMPL is able to stimulate both arms (neutralizing antibody and effector mediated immunity (DTH) of the immune system; however, Van Wijnendale does not teach or suggest that 3-DMPL is suitable for use in allergen formulation, (4) the '862 patent teaches a therapeutic composition comprising candidate flea saliva proteins, and excipient and an adjuvant and a carrier. However, there is no mention of 3-DMPL nor of tyrosine in this document, (5) there is no clear evidence of an unexpected result that would establish the nonobviousness of the present invention.

However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145. Further, the '862 patent teaches a therapeutic composition comprising un modified allergen such as isolated flea saliva protein and an adjuvant such as Ribi adjuvant from Ribi ImmunoCHem, which is 3-DMPL that enhances the immune response to any antigen (See column 42, line 20-35, claims 22 and 24 of '862, in particular) as evidence by the '110 patent (See column 1, lines 11-14, in particular) or the '632 patent that preferentially stimulates IgG2a and TH_1 response (see column 1, line 14-17, and column 1, lines 37, in particular).

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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August 26, 2002

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